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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,495	02/28/2002	Chihiro Kusunoki	SHIMO13	2089

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EXAMINER	
LIETO, LOUIS D	

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 03/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/937,495	KUSUNOKI ET AL.	
	Examiner	Art Unit	
	Louis D. Lieto	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *25 January 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-23* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's response filed on 1/25/2005 is acknowledged. Claims 15-23 are pending. Claims 1-14 have been cancelled, new claims 15-23 have been added. Claims 15-23 are under consideration. The sections of 35 U.S.C. not included in this office action can be found in a previous office action. An action on the merits follows.

Sequence Compliance

The objection of lack of sequence compliance is withdrawn in view of applicants submission of a CRF and paper listing SEQ ID NO:1.

Specification

The objection over the specification is withdrawn in view of applicant's amendment to the specification to remove all references to figures 1 and 2 of the drawings.

Claim Rejections - 35 USC § 112

The rejection of claims 1-14 under 35 U.S.C 112, first paragraph for lack of enablement is withdrawn in view of applicant's cancellation of claims 1-14.

New claims 15-23 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of producing a monoclonal antibody, wherein a B cell from a transgenic mouse, which expresses human antibodies but does not express mouse antibodies, is fused with a myeloma cell line to obtain a hybridoma , wherein the hybridoma comprises a rearranged immunoglobulin heavy chain nucleotide sequence which expresses a heavy chain polypeptide, and a rearranged immunoglobulin

light chain nucleotide sequence which expresses a light chain polypeptide; introducing into the hybridoma an exogenous nucleotide sequence which encodes a heavy chain polypeptide identical to the heavy chain polypeptide expressed by the endogenous immunoglobulin heavy chain to thereby obtain a transformant hybridoma transformed with the exogenous nucleotide Sequence; culturing the transformant in a cell culture medium; and obtaining a monoclonal antibody produced by the transformant, does not reasonably provide enablement for a method of producing a monoclonal antibody, comprising the steps of: fusing a B cell of a transgenic mouse with an immortal cell line to obtain a hybridoma , wherein the hybridoma comprises a rearranged immunoglobulin heavy chain nucleotide sequence which expresses a heavy chain polypeptide, and a rearranged immunoglobulin light chain nucleotide sequence which expresses a light chain polypeptide; introducing into the hybridoma an exogenous nucleotide sequence which encodes a heavy chain polypeptide identical to the heavy chain polypeptide expressed by the endogenous immunoglobulin heavy chain to thereby obtain a transformant hybridoma transformed with the exogenous nucleotide Sequence; culturing the transformant in a cell culture medium; and obtaining a monoclonal antibody produced by the transformant. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The rejection of new claims 15-23 is necessitated by their addition.

The new claims encompass a method of producing a monoclonal antibody, comprising fusing any B cell from any transgenic mouse with any immortal cell line to obtain a hybridoma, which comprises a rearranged immunoglobulin heavy chain nucleotide sequence, which expresses a heavy chain polypeptide, and a rearranged

immunoglobulin light chain nucleotide sequence which expresses a light chain polypeptide. Wherein the hybridoma is transformed with an exogenous nucleotide sequence encoding a polypeptide identical to the heavy chain polypeptide expressed by the hybridoma, and where the exogenous nucleotide sequence may further comprise a DHFR gene.

The specification does not provide any guidance on how to produce hybridomas by fusing a B cell with any immortal cell line other than a myeloma cell line. Immortal cell lines include, fibroblasts, jurkat cells and antibody producing B cell lymphoma cell lines, amongst others. The only working example in the specification teaches fusing a B cell with a myeloma cell line (NSO-bs12) incapable of producing antibodies (Specification pg. 21). The art of record only teaches that hybridomas can be predictably made by fusing B cells with hybridomas {Margulies et al. (2005) J. Immunology. 174:2451-2452}. Further, if the B cell of interest was fused with an antibody producing B cell lymphoma cell lines then the cells would produce multiple antibodies, which would not fulfill the intended use of the invention, to enhance the production of monoclonal antibodies. Given the lack of guidance in the specification on how to produce hybridomas by fusing a B cell with any immortal cell line except a myeloma cell line, and the lack of teachings in the art that hybridomas can be predictably produced by fusing a B cell with any immortal cell line, the skilled practitioner in the art would be unable to predict how to practice the claimed invention, except a method of producing a monoclonal antibody, wherein a B cell from a transgenic mouse, which expresses human antibodies but does not express mouse antibodies, is fused with a myeloma cell line to obtain a hybridoma , wherein the hybridoma comprises a rearranged immunoglobulin heavy chain nucleotide

sequence which expresses a heavy chain polypeptide, and a rearranged immunoglobulin light chain nucleotide sequence which expresses a light chain polypeptide; introducing into the hybridoma an exogenous nucleotide sequence which encodes a heavy chain polypeptide identical to the heavy chain polypeptide expressed by the endogenous immunoglobulin heavy chain to thereby obtain a transformant hybridoma transformed with the exogenous nucleotide Sequence; culturing the transformant in a cell culture medium; and obtaining a monoclonal antibody produced by the transformant, without undue and extensive experimentation

Claim Rejections - 35 USC § 103

The rejection of amended claims 1-14 under 35 U.S.C 102 (a) is withdrawn in view of their cancellation.

New claims 15-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent application No. US 2003/0153039 (8/14/2003), hereafter referred to Wood[1] et al., **or** US Patent No. 6,475,787 (11/5/2002), hereafter referred to Wood[2] et al., in view of Mendez et al. {Mendez et al., (1997) Nature Genetics. 15:146-186}. The rejection of new claims 15-23 is necessitated by their addition.

Wood[1] et al. teaches a method for producing a monoclonal antibody by introducing into a hybridoma containing an exogenous rearranged immunoglobulin heavy chain and an exogenous rearranged immunoglobulin light chain, a third exogenous DNA corresponding to the DNA encoding the immunoglobulin heavy chain, the culturing of said cell and the production of a functional monoclonal antibody (Wood[1] et al., pg. 5, col. 2, claims 4,5 and 6). Specifically, Wood et al., teaches a mammalian B-cell hybridoma

comprising DNA encoding an immunoglobulin heavy chain and an immunoglobulin light chain (Wood[1] et al., pgph 0013; pgph 0021; Wood[2] et al., col. 3, section II col. 4, pgph 3) and the introduction of a DNA encoding the identical immunoglobulin heavy chain (Wood[1] et al, pgph 0024; Wood[2] et al, col. 5, pgph 1). Wood et al. provides guidance that the DNA encoding an immunoglobulin heavy chain and an immunoglobulin light chain can be from any animal, which includes humans as well as non-human mammals, as well as genetically engineered chains that would comprise a mouse-human fusion antibody (Wood[1] et al., pgph 0010; pgph 0012; Wood[2] et al., col. 2, pgph 4; col. 3, section I). Further, Wood et al. teaches that the DNA encoding the immunoglobulin heavy chain comprises an amplifiable marker such as dihydrofolate reductase (DHFR) (Wood[1] et al., pgph 0007; Wood[2] et al., col. 2, pgph 1). Wood et al. teaches the culture of said cells and measurement of the monoclonal antibody (Wood[1] et al., pg. 4, examples 3 and 4; Wood[2] et al., col. 7&8, examples 3 and 4). Wood et al. teaches that the object of the invention is to improve the levels of antibody expression (Wood[1] et al., pgph 0006; Wood[2] et al., col. 1, pgph 6), specifically through the optimization of heavy chain gene copy numbers (Wood[1] et al., pgph 0008; Wood[2] et al., col. 2, pgph 2). Wood et al. does not teach that the cell is derived from a transgenic non-human mammal or that it contains endogenous immunoglobulin heavy and light chains that encode a secreted antibody.

Mendez et al., supplements the teachings of Wood[2] et al. by providing guidance on a transgenic mouse containing endogenous human DNA encoding heavy and light chains that undergo B cell specific rearrangement and produces human antibodies (Mendez et al., pg. 146, col. 2 pgph 2). Further, Mendez et al. teaches transgenic mouse B cell hybridomas (Mendez et al., pg. 151, col. 1 pgph 2).

Based on the motivation of Wood et al. that the antibody production of B cell hybridomas can be increased by transfecting them with an immunoglobulin heavy chain it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to apply the teachings of Wood et al. to any b-cell hybridomas with endogenous rearranged heavy and light chains including the transgenic mouse B cell hybridoma taught by Mendez et al.

The person of ordinary skill in the art would have been motivated to make this modification in order to increase the antibody production of B cell hybridomas and would reasonably be expected to succeed because Wood et al. has shown that this method works to increase antibody production in mammalian cells, which contain an immunoglobulin heavy chain and an immunoglobulin light chain.

Applicant's arguments filed on 1/25/2005 have been fully considered but they are not persuasive. Applicant argues that: 1) it would not be obvious to combine the references in the manner suggested in the absence of the teachings provided by the applicants; 2) the claimed invention provides improved unexpected results; and 3) new claims 15-23 clearly distinguish the invention from the cited reference.

The new claims encompass a method of producing a monoclonal antibody, comprising fusing any B cell from any transgenic mouse with any immortal cell line to obtain a hybridoma, which comprises a rearranged immunoglobulin heavy chain nucleotide sequence, which expresses a heavy chain polypeptide, and a rearranged immunoglobulin light chain nucleotide sequence which expresses a light chain polypeptide. Wherein the hybridoma is transformed with an exogenous nucleotide sequence encoding a polypeptide identical to the heavy chain polypeptide expressed by

the hybridoma, and where the exogenous nucleotide sequence may further comprise a DHFR gene.

In regards to applicant's first argument that it would not be obvious to combine the references in the manner suggested in the absence of the teachings provided by the applicants, it is noted that applicants do not provide any supporting statement for their contention. As was stated in the previous office action Wood et al. teaches a method of producing monoclonal antibodies by transforming a hybridoma with an exogenous DNA corresponding to the DNA encoding the immunoglobulin heavy chain, the culturing of said cell and the production of a functional monoclonal antibody (Wood[1] et al., pg. 5, col. 2, claims 4,5 and 6). Specifically, Wood et al., teaches a mammalian B-cell hybridoma comprising DNA encoding an immunoglobulin heavy chain and an immunoglobulin light chain (Wood[1] et al., pgph 0013; pgph 0021; Wood[2] et al., col. 3, section II col. 4, pgph 3) and the introduction of a DNA encoding the identical immunoglobulin heavy chain (Wood[1] et al, pgph 0024; Wood[2] et al, col. 5, pgph 1). Wood et al. provides guidance that the DNA encoding an immunoglobulin heavy chain and an immunoglobulin light chain can be from any animal, which includes humans as well as non-human mammals, as well as genetically engineered chains that would comprise a mouse-human fusion antibody (Wood[1] et al., pgph 0010; pgph 0012; Wood[2] et al., col. 2, pgph 4; col. 3, section I). Further, Wood et al. teaches that the DNA encoding the immunoglobulin heavy chain comprises an amplifiable marker such as dihydrofolate reductase (DHFR). Wood et al. teaches that his motivation for transforming the hybridomas was to produce high expression levels of monoclonal antibodies from the hybridoma by optimizing the gene copy numbers of the heavy chain (Wood[1] et al, pgph 008; Wood[2] et al, col. 2, pgph 2).

Therefore the teachings provided by the applicants are not required to motivate the skilled practitioner to apply the method taught by Wood et al. to the hybridomas taught by Mendez et al.

Second, applicant argues that the claimed invention provides improved . unexpected results. Applicant goes on to state that immunoglobulin heavy chain production from hybridomas is often unstable in comparison to the light chain. Applicant further notes that the amount of monoclonal antibodies is significantly increased in recombinant hybridomas by introducing a nucleic acid that encodes the hybridomas endogenous heavy chain, thus boosting the copy number of the heavy chain. Further applicant notes that the amount could be increased further still by introducing a gene amplification gene such as DHFR. However, in view of the method taught by Wood et al., of increasing heavy chain gene copy number in hybridomas in order to increase monoclonal antibody production, an artisan would have expected to increase production of a monoclonal antibody by increasing heavy chain copy number. Except for stating that applicants had unexpected results, applicant did not provide any evidence or discuss as to what was the unexpected result and why it was unexpected.

Third, applicant argues new claims 15-23 clearly distinguish the invention from the cited reference. However, new claims 15-23 continue to be drawn to an invention rendered obvious by Wood et al. and Mendez et al. for the reasons stated above and in the prior office action.

No claims Allowed

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Lou Lieto whose telephone number is (571) 272-2932. The examiner can normally be reached on Monday-Friday, 9am-5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is (571)-272-0735. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Patent applicants with problems or questions regarding electronic images that can be viewed in the PAIR can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent

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